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Consumption of Saturated Fat Impairs the Anti-Inflammatory Properties of High-Density Lipoproteins and Endothelial Function

Stephen J. Nicholls, MBBS, PhD, FRACP, FACC,*† Pia Lundman, MD, PhD, FESC,*‡§ Jason A. Harmer, BSc (Hons),‡ Belinda Cutri, BMedSc (Hons),* Kaye A. Griffiths, DMU,‡ Kerry-Anne Rye, PhD,* Philip J. Barter, MBBS, PhD, FRACP,*‖ David S. Celermajer, MBBS, PhD, FRACP*‡‖

Sydney and Adelaide, Australia; and Stockholm, Sweden

OBJECTIVES The purpose of this study was to investigate the influence of dietary fatty acids on the anti-inflammatory properties of high-density lipoproteins (HDL) and vascular function.

BACKGROUND The effect of dietary fatty acids on atherogenesis remains uncertain.

METHODS Fourteen adults consumed an isocaloric meal containing either a polyunsaturated or a saturated fat on 2 occasions. The effects of post-prandial HDL on endothelial cell expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) were determined. Flow-mediated dilation (FMD) and microvascular reactivity were assessed before and 3 and 6 h after the meal.

RESULTS Plasma triglycerides, insulin, and nonesterified fatty acids rose after the meals. The HDL collected 6 h after the saturated meal were less effective than HDL isolated from fasting plasma in terms of their ability to inhibit expression of ICAM-1 and VCAM-1, whereas HDL collected 6 h after the polyunsaturated meal had an inhibitory activity that was greater than that of HDL collected from fasting plasma ($p < 0.004$ and $p = 0.01$ for comparison of effect of meals on ICAM-1 and VCAM-1, respectively). Post-hyperemic microvascular flow significantly increased at 3 h after the polyunsaturated meal by 45 ± 14% and by 21 ± 11% after the saturated meal. The FMD decreased 3 h after the saturated meal by 2.2 ± 0.9% ($p < 0.05$ compared with baseline) and by 0.9 ± 1% after the polyunsaturated meal.

CONCLUSIONS Consumption of a saturated fat reduces the anti-inflammatory potential of HDL and impairs arterial endothelial function. In contrast, the anti-inflammatory activity of HDL improves after consumption of polyunsaturated fat. These findings highlight novel mechanisms by which different dietary fatty acids may influence key atherogenic processes. (J Am Coll Cardiol 2006;48:715–20) © 2006 by the American College of Cardiology Foundation

Fatty acid composition has a profound impact on the influence that dietary fat exerts on cardiovascular risk. Population (1) and animal (2) studies have reported that consumption of saturated fat promotes atherosclerosis, whereas polyunsaturated and monounsaturated fats are potentially protective.

In addition to influencing the atherogenicity of the lipid profile (3), it has been suggested that fatty acids may directly influence pathologic events in the artery that promote atheroma formation (4). A pivotal target for modulation is the endothelium. Endothelial dysfunction is a key early event in atherogenesis and occurs early in populations consuming a Western diet (5). It is therefore important to define the effect that different dietary fats have on endothelial biology.

The aim of this study was to define the effect of consuming a single high-fat meal, differing in fatty acid composition, on the ability of high-density lipoproteins (HDLs) to inhibit the expression of proinflammatory adhesion molecules by endothelial cells and on large and small vessel function.

METHODS

Experimental protocol. The study was approved by the ethics committee of the Central Sydney Area Health Service. Subjects, aged 18 to 40 years, without cardiovascular risk factors or established cardiovascular disease, provided written informed consent and attended after an overnight fast on 2 occasions, separated by 1 month. Subjects consumed 1 of 2 isocaloric meals comprising a slice of carrot cake and a milkshake containing 1 g of fat/kg of body weight. The first meal contained safflower oil (fatty acid composition: 75% polyunsaturated, 13.6% monounsaturated, and 8.8% saturated fat). The second meal contained coconut oil (fatty acid composition: 89.6% saturated fat, 5.8% monounsaturated, and 1.9% polyunsaturated fat). The order of meals ingested was determined by random allocation and was blinded to the investigators. Female subjects attended

From *The Heart Research Institute, Sydney, Australia; †Department of Medicine, University of Adelaide, Adelaide, Australia; ‡Department of Cardiology, Royal Prince Alfred Hospital, Sydney, Australia; §Division of Medicine, Karolinska Institutet, Danderyd University Hospital, Stockholm, Sweden; and the ‖Department of Medicine, University of Sydney, Sydney, Australia. Supported by a Pfizer Cardiovascular Lipid award. Dr. Nicholls is supported by a postgraduate research scholarship from the National Heart Foundation of Australia. Dr. Lundman is supported by postdoctoral scholarships from the Swedish Heart and Lung Foundation, Throne-Holst Foundation, Swedish Society of Medicine, and Swedish Society of Cardiology. Dr. Rye is a National Heart Foundation of Australia Principal Research Fellow. Drs. Celermajer, Rye, and Barter are supported by grant 222722 from the National Health and Medical Research Council of Australia.

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Abbreviations and Acronyms

apoA-I = apolipoprotein A-I
FMD = flow-mediated dilation
HDL = high-density lipoprotein
ICAM-1 = intercellular adhesion molecule 1
VCAM-1 = vascular cell adhesion molecule 1

within 7 days from the commencement of menstruation to control for the effect of hormonal variation during the menstrual cycle on vascular function. Venous blood was collected and assessments of venous plethysmography followed by brachial artery reactivity were performed in the fasting state and 3 and 6 h after the meal.

Characterization of HDL. The HDL (1.063 > density >1.21 g/ml) were isolated from plasma by sequential ultracentrifugation and dialyzed against endotoxin-free phosphate-buffered solution (6). Cholesterol, triglyceride, phospholipid (7), and protein (8) composition of HDL was determined by enzymatic assay. Apolipoprotein A-I (apoA-I) composition was determined immunoturbidometrically using a sheep antihuman apoA-I antibody (9). The HDL size was determined by nondenaturating polyacrylamide gel electrophoresis. Surface charge of HDL was determined by agarose gel electrophoresis.

Determination of cell surface adhesion molecule expression by endothelial cells. Human umbilical vein endothelial cells were isolated (10) and incubated with HDL samples at a concentration of 2, 4, or 8 μmol/l apoA-I in media containing 10% heat-inactivated serum for 16 h at 37°C in 5% CO_2. Cells were incubated for a further 5 h in the basal or stimulated state following the addition of tumor necrosis factor-alpha (0.2 ng/ml). The cell surface expression of adhesion molecules was assessed with an enzyme-linked immunosorbent assay technique (11). Cellular viability was determined to be greater than 95% by trypan blue exclusion.

Effect on vascular reactivity. Forearm blood flow in the left forearm was determined by venous occlusion strain gauge plethysmography (Hokanson, Bellevue, Washington) as previously described (12). Post-ischemic volume was determined as the area under the flow versus time curve for the first 115 s after release of suprasystolic pressure.

Brachial artery reactivity was assessed by measuring end-diastolic vessel diameter from B-mode ultrasound images using an ATL HDL 5000 machine (Philips, Bothell, Washington) as previously described (13). Brachial artery diameter was measured at rest, during reactive hyperemia, and after administration of 400 μg sublingual glyceryl trinitrate. Vessel diameter after reactive hyperemia and administration of sublingual nitrate was expressed as the percentage relative to the average resting diameter.

Plasma analyses. Plasma was stored at −80°C until analyzed. Plasma concentrations of cholesterol, triglyceride, HDL-cholesterol and nonesterified fatty acids were determined by enzymatic assays. The HDL-cholesterol was determined following precipitation of apoB containing lipoproteins with polyethylene glycol. Low-density lipoprotein cholesterol was calculated using the Friedewald equation. Plasma insulin levels were determined by a microparticle enzyme immunometric assay (MEIMA) (Abbott, Tokyo, Japan).

Data analysis. All results are expressed as mean ± SEM. Statistical comparisons were performed using a generalized linear model for repeated measures using the mixed model procedure in SAS (SAS Institute, Cary, North Carolina). This model determined whether the meal type had an effect on outcome. Meal type and time of measurement were used as fixed effects and an interaction between the two was tested. Comparisons are presented for differences between time points, meals and for the meal-time point interaction. To ensure that sequence or carry-over effects did not confound the cross-over studies, subjects were divided into 2 groups based on sequence of meal ingested (polyunsaturated then saturated or saturated then polyunsaturated groups). Given the small group sizes and long interval between meals, order effect was unlikely to be a confounding factor. Group was added to the analyses as an independent variable. There were no group × meal, group × time, or group × meal × time interactions. Given that the tests for order effects were not significant, the simplified models without order terms are reported throughout the manuscript. A value of $p < 0.05$ was determined to be statistically significant.

RESULTS

Clinical and biochemical characteristics. Fourteen healthy subjects (mean age 29.5 ± 2.3 years, mean body mass index 23.6 ± 0.8 kg/m^2, 8 males) participated. Both meals were followed by an increase in plasma levels of triglyceride and insulin at 3 h and nonesterified fatty acid levels at 6 h (Table 1). The chemical composition (Table 2), particle size, and electrophoretic mobility of isolated HDL did not change following consumption of either meal.

Effect on adhesion molecule expression. The presence of HDL collected after a saturated fat meal was accompanied by a higher level of expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1) in the activated cells compared with HDL from the fasting state. In contrast, HDL collected after the polyunsaturated fat meal was accompanied by a significantly lower level of expression of ICAM-1 and VCAM-1 (apparent at HDL apoA-I concentrations of 2, 4, and 8 μmol/l). The cytokine-induced expression of ICAM-1 and VCAM-1 was higher than when the cells were incubated in the presence of HDL collected 6 h after the saturated compared with the polyunsaturated fat meal (Fig. 1).

Effect on vascular reactivity. Post-hyperemic forearm blood flow increased 3 h after consumption of the polyunsaturated fat by 45 ± 14% and by 21 ± 11% after the saturated fat meal (Table 3). Flow-mediated dilation (FMD) decreased

Table 1. Biochemical Parameters at Baseline and After a Meal Containing a Polyunsaturated or a Saturated Fat

	Baseline	3 h	6 h	p Value Comparison Between Time Points	p Value Comparison Between Meals	Meal-Time Point Interaction
TC (mmol/l)						
Polyunsaturated	4.55 ± 0.12	4.79 ± 0.23	4.94 ± 0.29	0.92	0.003	0.48
Saturated	4.37 ± 0.23	4.43 ± 0.28	4.46 ± 0.26			
LDL-C (mmol/l)						
Polyunsaturated	2.43 ± 0.23	2.60 ± 0.30	2.69 ± 0.30	0.17	0.04	0.94
Saturated	2.21 ± 0.23	2.35 ± 0.30	2.36 ± 0.26			
HDL-C (mmol/l)						
Polyunsaturated	1.70 ± 0.20	1.74 ± 0.20	1.90 ± 0.28	0.34	0.19	0.70
Saturated	1.70 ± 0.20	1.59 ± 0.19	1.64 ± 0.21			
Triglyceride (mmol/l)						
Polyunsaturated	0.95 ± 0.08	1.47 ± 0.3	1.08 ± 0.16	0.004	0.22	0.46
Saturated	1.01 ± 0.12	1.32 ± 0.23	1.18 ± 0.15			
Insulin (pmol/l)						
Polyunsaturated	28.8 ± 4.9	51.2 ± 11.3	32.8 ± 8.4	0.0002	0.52	0.95
Saturated	32.1 ± 4.5	46.0 ± 7.5	35.2 ± 7.6			
NEFA (μmol/l)						
Polyunsaturated	366.1 ± 52.6	362.5 ± 82.4	473.6 ± 70.6	<0.0001	0.18	0.07
Saturated	353.0 ± 50.4	376.3 ± 75.6	627.0 ± 24.6			

Results expressed as mean ± SEM.
HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; NEFA = nonesterified fatty acid; TC = total cholesterol.

at 3 h following consumption of the saturated meal ($p < 0.05$ compared with pre-meal) but not 3 h after the polyunsaturated meal (p = NS compared with the fasting state), although the difference in post-prandial change in FMD between the meals just failed to meet the conventional criteria for statistical significance. The FMD at 6 h after both meals did not significantly differ compared with the fasted state (Table 4), There was no significant change in the vessel size, estimated flow within the brachial artery, and glyceryl trinitrate response following both meals.

DISCUSSION

This study demonstrates that the fatty acid composition of a single high-fat meal modifies the ability of HDL to protect the endothelium and vascular reactivity in healthy subjects. Consuming a polyunsaturated fat enhanced, and a saturated fat meal reduced, the anti-inflammatory properties of HDL. A nonsignificant trend toward impairment of endothelium-dependent vascular reactivity in conduit arteries was also demonstrated after the saturated fat meal. These findings highlight potential mechanisms by which dietary fatty acids might influence atherogenesis.

It is well documented that HDL possess anti-inflammatory properties. Native (10) and reconstituted (14) forms inhibit in vitro expression of adhesion molecules by cytokine-stimulated endothelial cells. The degree of saturation of the fatty acid in the *sn-2* position of the phosphatidylcholine had a marked influence on the ability of reconstituted HDL to inhibit VCAM-1 expression by activated endothelial cells (15). This observation paralleled the effect of fatty acids on adhesion molecule expression by activated endothelial cells (16) and raised the possibility that variations in the phospholipid composition of HDL may have contributed to the observed wide variation in inhibitory activity of HDL isolated from different human subjects (17).

The current study indicates that dietary fat composition has a substantial influence on the anti-inflammatory potential of HDL isolated from post-prandial human plasma. It may contribute to the finding that the systemic level of soluble adhesion molecules varies with the consumption of different fatty acids (18). The mechanism of the effect is uncertain, although it may be the result of minor changes in the phospholipid composition of the HDL. The composition of phospholipids in chylomicrons is influenced by the

Table 2. High-Density Lipoprotein Composition at Baseline and After Consumption of a Meal Containing a Polyunsaturated or a Saturated Fat

	Protein	Phospholipid	Triglyceride	Cholesterol Ester	Unesterified Cholesterol
Polyunsaturated					
Baseline	50.5 ± 1.9	27.9 ± 1.6	2.2 ± 0.3	16.2 ± 1	3.3 ± 0.3
3 h	50.2 ± 1.7	29.2 ± 1	2.4 ± 0.4	15.1 ± 0.8	3.2 ± 0.2
6 h	51.8 ± 1.3	27.1 ± 1.1	2.5 ± 0.3	15.5 ± 0.7	3.2 ± 0.2
Saturated					
Baseline	53.1 ± 1.4	26.6 ± 1.6	2.6 ± 0.3	14.5 ± 0.8	3.3 ± 0.3
3 h	51.3 ± 1.6	27.7 ± 1.4	2.1 ± 0.3	16.2 ± 1.2	2.7 ± 0.2
6 h	49.4 ± 1.1	29.9 ± 1	2.2 ± 0.3	15.5 ± 1	3.1 ± 0.2

Results expressed as percentage of total molar mass (mean ± SEM).

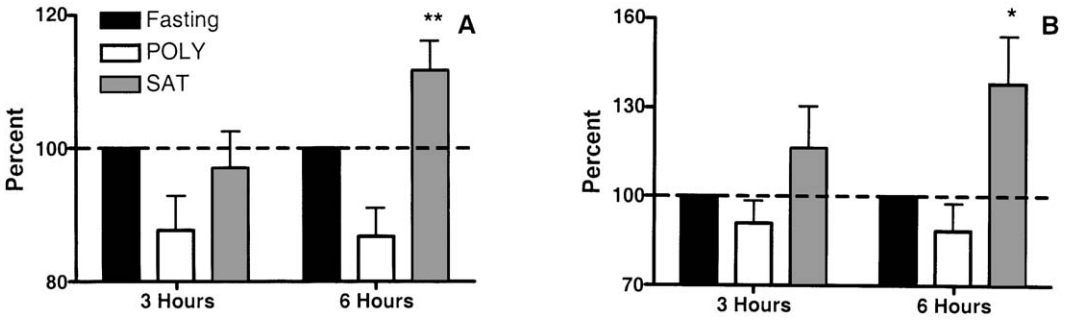

Figure 1. Expression of intercellular adhesion molecule-1 (ICAM-1) **(A)** and vascular cell adhesion molecule-1 (VCAM-1) **(B)** by activated human umbilical vein endothelial cells after incubation with high-density lipoprotein (HDL) isolated after a meal enriched with a polyunsaturated **(open bars)** or saturated **(gray bars)** fat. Cells were incubated with HDL at an apolipoprotein A-I concentration of 8 μmol/l. Results are expressed as percentage of expression in the presence of HDL isolated from fasting blood **(solid bars)** (mean ± SEM). For difference between the meals: *p = 0.007; **p = 0.005. A significant meal-time period interaction was found for both ICAM-1 (p = 0.01) and VCAM-1 (p = 0.04).

composition of consumed fat, and phospholipids are transferred from chylomicrons to HDL (19). Therefore, it would not be surprising if there were changes in the HDL phospholipid composition after the meal.

In a complementary finding, the present study also demonstrated that altering the fatty acid composition of a meal had a potential influence on vascular function in large vessels. Consuming a saturated fat was associated with a significant post-prandial impairment of vascular reactivity, whereas no such change was observed after eating the isocaloric polyunsaturated meal. There was a trend toward a greater post-prandial impairment seen after the consumption of the saturated compared with the polyunsaturated fat. A similar finding has been reported in some (20,21), but not all (12), studies that have investigated the effect of consuming a fatty meal on endothelial function. Vogel et al. (22) have reported that consumption of a meal high in monounsaturated but not polyunsaturated fats was associated with a reduction in FMD during the post-prandial period in healthy volunteers. In contrast, Raitakari et al. (12) found that a high-fat meal resulted in an increase in resting flow and post-ischemic hyperemia in the microvasculature, without any changes in FMD. The reason for such discrepancies is uncertain but may be related, in part, to a lack of standardization of the ingested meal and protocol used to assess vascular function.

Similarly, variable relationships have been reported between longer-term consumption of dietary fats and endothelial function in subjects with or without vascular risk factors (23–25). It has been recently reported that adoption of a saturated fat-enriched diet over a 3-week period was associated with an impairment of FMD and elevation of plasma levels of P-selectin (26) in healthy young adults.

In contrast, consumption of polyunsaturated fats was associated with an increase in microvascular blood flow. This supports reports that demonstrated an increase in microvascular reactivity, which correlated with the postprandial rise in circulating insulin levels (12). Post-ischemic hyperemia is not thought to be a predominantly endothelium-dependent phenomenon. Rather, it indicates the maximum functional vasodilator capacity of tissue and is likely to result from the interaction of a number of factors, including prostaglandins, lactic acid, pH, adenosine, carbon dioxide, potassium, and nitric oxide (27,28). Thus it is likely that the complex influence of dietary fatty acids on the vasculature is likely to be mediated by a multitude of factors in addition to nitric oxide.

It is unclear whether altering dietary fat composition influences other functions of HDL. Our current results were obtained in a modest cohort of normal subjects, and extrapolation to subjects with atherosclerosis or with risk factors should be made with caution. Although the differ-

Table 3. Plethysmography Parameters at Baseline and After a Meal Containing a Polyunsaturated or a Saturated Fat

	Baseline	3 h	6 h	p Value Comparison Between Time Points	p Value Comparison Between Meals	Meal-Time Point Interaction
FBF_{rest} (ml/min/100 ml)						
Polyunsaturated	1.4 ± 0.2	2.0 ± 0.2	1.7 ± 0.2	0.001	0.32	0.17
Saturated	1.5 ± 0.1	1.8 ± 0.2	1.5 ± 0.1			
Peak flow (ml/min/100 ml)						
Polyunsaturated	19.7 ± 0.8	19.9 ± 1.3	19.1 ± 1.2	0.73	0.47	0.84
Saturated	20.6 ± 1.1	19.9 ± 1.7	19.8 ± 1.2			
Total hyperemia (ml/100 ml)						
Polyunsaturated	10.9 ± 1.1	15.6 ± 2.1	12.2 ± 1.4	0.02	0.26	0.49
Saturated	13.6 ± 1.9	15.5 ± 2.3	13.0 ± 1.9			

Results expressed as mean ± SEM.
FBF = forearm blood flow.

Table 4. Brachial Artery Parameters at Baseline and After a Meal Containing a Polyunsaturated or a Saturated Fat

	Baseline	3 h	6 h	p Value Comparison Between Time Points	p Value Comparison Between Meals	Meal-Time Point Interaction
Flow-mediated dilation (%)						
Polyunsaturated	5.2 ± 1.1	4.3 ± 1.0	4.8 ± 1.2	0.07	0.08	0.62
Saturated	6.9 ± 0.9	4.7 ± 0.8	6.2 ± 1.5			
Vessel size (mm)						
Polyunsaturated	3.8 ± 0.2	3.8 ± 0.2	3.8 ± 0.2	0.07	0.82	0.65
Saturated	3.7 ± 0.2	3.8 ± 0.2	3.8 ± 0.2			
Flow (ml/min)						
Polyunsaturated	63.1 ± 12.1	70.4 ± 15.7	64.3 ± 14.0	0.73	0.39	0.99
Saturated	72.6 ± 18.4	81.4 ± 18.9	73.3 ± 15.8			
Total hyperemia (ml/100 ml)						
Polyunsaturated	955.5 ± 127.8	972.4 ± 159.5	1,147.8 ± 201.0	0.46	0.27	0.76
Saturated	1,365.4 ± 547.8	1,005.9 ± 230.4	1,680.2 ± 794.3			

Results expressed as mean ± SEM.

ences in FMD, arterial diameter, and flow at baseline between the groups were nonsignificant, it is possible that "regression to the mean" may have contributed to some of the FMD reduction observed after consumption of the saturated fat (although all analyses were "blinded" to meal assignment and timing). Although the meals had different effects on hyperemia in conduit and resistance vessels, the direction of the meal-related changes was similar in large and small vessel studies, with a trend toward a greater increase in flow after consumption of polyunsaturated fats.

In summary, the present study raises the possibility that the differential effects of dietary fats on the anti-inflammatory potential of HDL and endothelial function may contribute to the apparent benefits of polyunsaturated over saturated diets observed in the epidemiologic literature.

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Reprint requests and correspondence: Prof. David Celermajer, Department of Cardiology, Royal Prince Alfred Hospital, Camperdown, NSW 2050, Australia. E-mail: david.celermajer@email.cs.nsw.gov.au.

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